

## M-1 – (1) Scientific Abstract

Cancer is a leading cause of death in the Western World. Approximately 1,200,000 new cases are expected to be diagnosed in 2000, with approximately 550,000 deaths expected (American Cancer Society, Inc. Surveillance Research, 2000). Although most patients die from disseminated cancer, a substantial number die due to complications of locally advanced disease. Furthermore, patients who die of metastases frequently also suffer the morbidity of advanced local disease.

Current cancer therapy includes surgery, chemotherapy, radiation therapy (RT), hormone therapy and immunotherapy. These treatment modalities, either alone or in combination, provide high degrees of local control in early stage disease but often fail in eradicating bulky tumors. The addition of gene transfer to currently available modalities provides the potential to improve local tumor control rates.

TNFERade™ biologic (AdEGR.TNF.11D) is an E1-, partial E3-, E4-, replication deficient, adenovirus serotype 5, gene transfer vector. The transgene in this vector is the cDNA for human tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Elements of the radiation inducible early growth response (Egr-1) promoter are ligated upstream from the transgene to allow for maximum expression of TNF- $\alpha$  only in the presence of ionizing radiation.

TNF- $\alpha$  is a human cytokine well known for its anti-tumor effects, and its ability to act synergistically with radiation therapy. It has been approved for use in Europe via isolated limb perfusion for the treatment of soft tissue sarcoma. Its wider use as an anti-cancer agent, however, has been limited by severe systemic side effects. It is proposed that a locally delivered gene transfer approach using the TNF- $\alpha$  gene would capitalize on these anti-tumor effects while limiting the systemic toxicity.

Studies with Ad5.Egr-TNF, a vector analogous to TNFERade™ biologic, have demonstrated efficacy and tolerability in a variety of animal models. Furthermore, these studies show a synergistic effect of combined treatment with TNFERade™ biologic and radiation resulting in a greater tumor response than seen with each individual treatment modality. No systemic side effects were reported and only mild local effects, including edema, fibrosis and small areas of necrosis, were observed.

Intratumoral administration of TNFERade™ biologic combined with radiation therapy provides a convenient means of delivering TNF- $\alpha$  locally, with the potential for an improved tumor response rate over radiation alone. Hopefully, this approach can provide a potent anti-cancer effect with an acceptable toxicity profile. The primary objectives of this investigation are: (1) to assess the safety and feasibility of intratumoral injection of TNFERade™ biologic in combination with radiation in patients with locally advanced, metastatic and recurrent solid tumors that have failed standard treatment and (2) to identify the site-specific maximum tolerated dose (MTD) of TNFERade™ biologic and radiation.